REMARKS

Favorable consideration of this application as presently amended is respectfully requested.

The new section to the specification, entitled "Cross-Reference to Related Applications," is inserted because the present application is a divisional of U.S. App. Serial No. 09/424,181. No new matter is added by this amendment.

The attached paper and computer readable copies of the Sequence Listing are submitted in compliance with 37 C.F.R. §§ 1.821-1.825. The contents of the paper and computer readable copies of the Sequence Listing are the same. No new matter is added by this addition to the specification.

The amendment to claim 9 is requested to place the claim in independent form. Support for the amendment to claim 9 is found in original claims 1 and 9, in the specification at page 26, lines 1-20 and structure E, as well as elsewhere through the application.

The amendment to claims 10 and 11 is requested so that the dependency of claims 10 and 11 reflects the amendments to claim 9.

Support for the newly added claim 20 is found in original claim 1, as well as elsewhere through the application.

The amendments to the claims 12, 14, and 19 are requested to remove the multiple dependencies. The amendments to claims 12, 14, and 19 are written to put the claims in non-multiple dependent format. Claim 21 is added to cover the dependency of original claims 15 and 19. No new matter has been added by these

amendments or by the new claims.

The amendments to claims 13 and 15 are to change the format of the claims. No new matter is added by these amendments.

Prompt and favorable consideration of this application on its merits is respectfully requested.

Respectfully submitted,

Mark J. Guttag
Reg. No. 33,057

Attachments:
Sequence Listing (paper and computer readable copies)

Jagtiani + Guttag
Democracy Square Business Center
10379-B Democracy Lane
Fairfax, Virginia 22030
703-591-2664

December 5, 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)
	)
ROGELJ, ET AL.	) **Examiner: To be assigned**
	)
SERIAL NUMBER: To be assigned, a Divisional of U.S. App. Serial No. 09/424,181, filed on November 10, 1999	) **Art Unit: To be assigned**
	)
FILED: CONCURRENTLY HEREWITH	)
	)
FOR: INHIBITION OF CELL SURFACE PROTEIN DISULFIDE ISOMERASE	) **Docket No: UNME-0115-1**

Director of U.S. Patent and Trademark Office
Washington, D.C. 20231

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Sir:

Below are the amendments in the accompanying Amendment for the above-identified application shown in redlined format:

IN THE SPECIFICATION:

Please amend the Specification, without prejudice or disclaimer, as indicated below:

Please add the paragraph at page 1, line 2, above the section entitled "Background of the Invention", the following new section and paragraph:

-- **CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a divisional of the following co-pending U.S. Patent Application, Serial No. 09/424,181, entitled "Inhibition of Cell Surface Protein Disulfide Isomerase," filed on May 3, 1999. The entire disclosure and contents of the above applications are hereby incorporated by reference. --

Please insert the attached Sequence Listing, page 1, at the end of the

Application.

Please delete the paragraph at page 1, line 19 to page 2, line 9 and substitute therefor the following paragraph:

PDI (protein disulfide isomerase) is a constitutive intracellular protein that is also found to be expressed on the surface of many mammalian cell types, including immune system cells, hepatocytes, and platelets. Like other members of the thyredoxin superfamily of proteins, PDI is a multifunctional redox-sensitive protein that catalyzes oxidation-reduction reactions via a vicinal dithiol-dependent disulfide-sulfhydryl interchange between its internal vicinal dithiol (Cys-Gly-His-Cys SEQ ID NO. 1) active sites and the disulfide bonds of its substrates to promote their reconfiguration. PDI recognizes the side chains of cysteine residues in its substrates, and it is its two vicinal dithiol groups, one or two on each of two identical PDI subunits, that are critical for its enzymatic isomerase function, in particular its broad specificity for correcting the configuration of a large spectrum of proteins as needed. For example, PDI is present in the endoplasmic reticulum of most cells, where it is believed to mediate co- and post-translational modifications of nascent proteins with incorrect sulfide bonds; it is also present in certain protein complexes such as triglyceride transfer protein complex (MTP) wherein it maintains the complex in a catalytically-active state and inhibits complex aggregation. Membrane PDI catalyzes the cleavage of disulfide bonds during the earliest stages of endocytosis, and activates diphtheria toxin by catalyzing cleavage of this disulfide-linked dimer. PDI also catalyzes the isomerization of thrombospondin (TSP) disulfide bonds, thereby profoundly modulating TSP-ligand binding activity. Both TSP and PDI are released by activated platelets; PDI is also released by degranulated neutrophils (J. Cell Physiol. 144:280, 1990).

Please delete the paragraph at page 6, lines 16 to 25 and substitute therefor the

following paragraph:

According to the invention, cell-surface PDI (csPDI) isomerase activity is effectively inhibited by thiol blocking agents (inhibitors) which covalently or non-covalently cross-link two or more free vicinal sulfhydryl groups of one or more PDI active site peptide sequences to form complexes stable in the cell environment. The -SH groups of the cysteine residues in the sequence Cys-Gly-His-Cys (SEQ ID NO. 1) are exemplary. The inhibitors are preferably highly selective for PDI vicinal sulfhydryls and have sufficient affinity for these groups to compete successfully with the ligand to be denied access to these sites and prevent PDI-mediated isomerization of its disulfide bonds and its consequent reconfiguration for undesired biological activity. The sequence of PDI is known (Nature 317:6034; 267, 1985) Herein, "csPDI" and "PDI" are used interchangeably unless otherwise noted.

Please delete the paragraph at page 12, lines 4 to 14 and substitute therefor the following paragraph:

Most of the inhibitors identified by the inventors to date, including cadmium, and trivalent arsenical and antimonial compounds work by blocking the vicinal cysteines in PDI active sites; however, some inhibitors may work by blocking PDI activity by a mechanism that is different from the thiol-mediated blockade of the Cys-Gly-His-Cys (SEQ ID NO. 1) active sites. The inhibitors are generally not cell-specific (unlike, for example, fMLP for which CHO and lymphocytes are receptor negative), and are selected as the application requires as described herein. Cell-membrane impermeable inhibitors are typically selected for applications requiring minimization of toxicity as are the dithiol and dithiol-specific inhibitors, as these tend to be efficacious at lower relative concentrations. Monothiol and/or cell-membrane permeable inhibitors are, however, useful in the practice of the invention and may prove equal or superior to dithiol inhibitors in

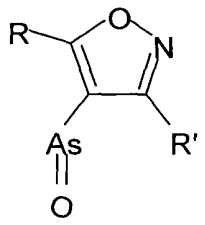
applications where a slight increase in cell toxicity is not a critical factor.

IN THE CLAIMS

Claims 1, 2, 3, 4, 5, 6, 7, 8, 16, 17 and 18 have been cancelled in the accompanying transmittal documents for the present application, without prejudice or disclaimer.

Please amend the claims, without prejudice or disclaimer, as indicated below:

9. (Amended) ~~An inhibitor according to Claim 1 of the~~ A compound having the following formula:



wherein at least one of R and R' is a charged ligand.

10. (Amended) ~~An inhibitor~~ The compound according to ~~Claim~~ claim 9, wherein the charged ligand contains at least one sulfonate group.

11. (Amended) ~~An inhibitor according to Claim 2 or~~ The compound according to claim 9, wherein one of R or R' is an uncharged H or C_1-C_6-alkyl ligand.

12. (Amended) A method for inhibiting PDI compounds exposing cells expressing PDI to a compound according to claim 9 ~~any one of Claims 1-8~~ in an amount sufficient to inhibit PDI activity.

13. (Amended) The method of ~~Claim~~ claim 12, wherein PDI activity is 35 measured by assaying L-selectin shedding from leucocytes or lymphocytes.

14. (Amended) A method for treating a mammal for a viral infection propagated by PDI-mediated virion entry into host cells comprising administering to the mammal ~~phenylarsine oxide (PAO) or a~~the compound of ~~according to any one of Claims 1-8~~claim 9 in an amount sufficient to inhibit viral propagation.

15. (Amended) The method of ~~Claim~~ claim 14, wherein the viral infection is an HIV infection.

19. (Amended) A method for determining optimum blood concentrations of a PDI inhibitor for treatment of a mammal for a viral infection ~~according to Claim 14 or 15,~~ comprising: admixing a blood sample with ~~PDI inhibitor~~the compound of claim 9 and assaying for leucocyte L-selectin shedding.

Please add the following new claims:

20. (New) The compound of claim 9, wherein said compound is a membrane impermeable inhibitor of protein disulfide isomerase (PDI).

21. (New) The method of claim 19, wherein the viral infection is an HIV +infection.